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ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/biological entities)

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1. Introduction

This guideline describes approaches to developing process and drug substance understanding and also provides guidance on what information should be provided in CTD sections 3.2.S.2.2 – 3.2.S.2.6. It provides further clarification on the principles and concepts described in ICH guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality Systems (Q10) as they pertain to the development and manufacture of drug substance.

A company can choose to follow different approaches in developing a drug substance. For the purpose of this guideline, the terms “traditional” and “enhanced” are used to differentiate two possible approaches. In a traditional approach, set points and operating ranges for process parameters are defined and the drug substance control strategy is typically based on demonstration of process reproducibility and testing to meet established acceptance criteria. In an enhanced approach, risk management and more extensive scientific knowledge are used to select process parameters and unit operations that impact critical quality attributes (CQAs) for evaluation in further studies to establish any design space(s) and control strategies applicable over the lifecycle of the drug substance. As discussed in ICH Q8 for drug product, a greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches. The degree of regulatory flexibility is generally predicated on the level of relevant scientific knowledge provided in the application for marketing authorisation.

Traditional and enhanced approaches are not mutually exclusive. A company can use either a traditional approach or an enhanced approach to drug substance development, or a combination of both.

2. Scope

This guideline is applicable to drug substances as defined in the Scope sections of ICH Guidelines Q6A and Q6B, but might also be appropriate for other types of products following consultation with the appropriate regulatory authorities. It is particularly relevant to the preparation and organisation of the contents of sections 3.2.S.2.2 – 3.2.S.2.6 of Module 3 of the Common Technical Document (ICH M4Q). The guideline does not apply to contents of submissions during the clinical research stages of drug development. Nevertheless, the development principles presented in this guideline are important to consider during the investigational stages.

Regional requirements for post-approval changes are not covered by this guideline.

3. Manufacturing Process Development

3.1. General Principles

The goal of manufacturing process development for the drug substance is to establish a commercial manufacturing process capable of consistently producing drug substance of the intended quality.

3.1.1. Drug Substance Quality Link to Drug Product

The intended quality of the drug substance should be determined through consideration of its use in the drug product as well as from knowledge and understanding of its physical, chemical, biological, and microbiological properties or characteristics, which can influence the development of the drug product (e.g., the solubility of the drug substance can affect the choice of dosage form). The Quality Target Product Profile (QTPP) and potential CQAs of the drug product (as defined in ICH Q8) can help identify

41 potential CQAs of the drug substance. Knowledge and understanding of the CQAs can evolve during
42 the course of development.

43 **3.1.2. Process Development Tools**

44 Quality Risk Management (QRM, as described in ICH Q9) can be used in a variety of activities including
45 assessing options for the design of the manufacturing process, assessing quality attributes and
46 manufacturing process parameters, and increasing the assurance of routinely achieving acceptable
47 quality results. Risk assessments can be carried out early in the development process and repeated as
48 greater knowledge and understanding become available. It is neither always appropriate nor always
49 necessary to use a formal risk management process (using recognised tools and/or internal
50 procedures, e.g., standard operating procedures). The use of informal risk management processes
51 (using empirical tools and/or internal procedures) can also be considered acceptable.

52 Knowledge management (as described in ICH Q10) can also facilitate manufacturing process
53 development. In this context, potential sources of information can include prior knowledge and
54 development studies. Prior knowledge can include established biological, chemical and engineering
55 principles and applied manufacturing experience. Data derived from relevant prior knowledge,
56 including platform manufacturing (see glossary) can be leveraged to support development of the
57 commercial process and expedite scientific understanding.

58 **3.1.3. Approaches to Development**

59 ICH Q8 recognises that "Strategies for product development vary from company to company and from
60 product to product. The approach to, and extent of, development can also vary and should be outlined
61 in the submission." These concepts apply equally to the development of the drug substance
62 manufacturing process. An applicant can choose either a traditional approach or an enhanced approach
63 to drug substance development, or a combination of both.

64 Manufacturing process development should include, at a minimum, the following elements:

- 65 • Identifying potential CQAs associated with the drug substance so that those characteristics having
66 an impact on product quality can be studied and controlled;
- 67 • Defining an appropriate manufacturing process;
- 68 • Defining a control strategy to ensure process performance and drug substance quality (see Section
69 6 on Control Strategy).

70 An enhanced approach to manufacturing process development would additionally include the following
71 elements:

- 72 • A systematic evaluation, understanding and refining of the manufacturing process, including;
 - 73 – Identifying, through e.g. prior knowledge, experimentation and risk assessment, the material
74 attributes and process parameters that can have an effect on drug substance CQAs;
 - 75 – Determining the functional relationships that link material attributes and process parameters to
76 drug substance CQAs;
- 77 • Using the enhanced approach in combination with QRM to establish an appropriate control strategy
78 which can, for example, include a proposal for a design space(s) and/or real-time release testing
79 (RTRT).

80 The increased knowledge and understanding obtained from taking an enhanced approach could
81 facilitate continual improvement and innovation throughout the product lifecycle (see ICH Q10).

82 **3.1.4. Drug Substance Critical Quality Attributes**

83 A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be
84 within an appropriate limit, range, or distribution to ensure the desired product quality. Potential drug
85 substance CQAs are used to guide process development. The list of potential CQAs can be modified as
86 drug substance knowledge and process understanding increase.

87 Drug substance CQAs typically include those properties or characteristics that affect identity, purity,
88 biological activity and stability. When physical properties are important with respect to *in vivo*
89 performance or drug product manufacture, these can be designated as CQAs. In the case of
90 biotechnological/biological products, most of the CQAs of the drug product are associated with the drug
91 substance and thus are a direct result of the design of the drug substance or its manufacturing
92 process.

93 Impurities are an important class of potential drug substance CQAs because of their potential impact
94 on drug product safety. For chemical entities, impurities can include organic impurities (including
95 potential genotoxic impurities), inorganic impurities, for example metal residues, and residual solvents
96 (see ICH Q6A, Q3A, and Q3C). For biotechnological/biological products, impurities may be process-
97 related or product-related (see ICH Q6B). Process-related impurities include: cell substrate-derived
98 impurities (e.g., Host Cell Proteins and DNA); cell culture-derived impurities (e.g., media components);
99 and downstream-derived impurities (e.g., column leachables). CQAs for biotechnology/biological
100 products should also include consideration of contaminants, as defined in Q6B, including all
101 adventitiously introduced materials not intended to be part of the manufacturing process (e.g.,
102 adventitious viral, bacterial, or mycoplasma contamination).

103 The identification of CQAs for complex products can be challenging. Biotechnological/biological
104 products, for example, typically possess such a large number of quality attributes that it might not be
105 possible to fully evaluate the impact on safety and efficacy of each one. Risk assessments can be
106 performed to rank or prioritise quality attributes. Prior knowledge can be used at the beginning of
107 development and assessments can be iteratively updated with development data (including data from
108 non-clinical and clinical studies) during the lifecycle. Knowledge regarding mechanism of action and
109 biological characterisation, such as studies evaluating structure-function relationships, can contribute
110 to the assessment of risk for some product attributes.

111 **3.1.5. Linking Material Attributes and Process Parameters to Drug** 112 **Substance CQAs**

113 The manufacturing process development program should identify which material attributes (e.g., of
114 raw materials, starting materials, reagents, solvents, process aids, intermediates) and process
115 parameters should be controlled. Risk assessment can help identify the material attributes and process
116 parameters with the potential for having an effect on drug substance CQAs. Those material attributes
117 and process parameters that are found to be important to drug substance quality should be addressed
118 by the control strategy.

119 The risk assessment to define the control strategy of materials upstream from the drug substance can
120 include an assessment of manufacturing process capability, attribute detectability, and severity of
121 impact as they relate to drug substance quality. For example, when assessing the link between an
122 impurity in a raw material or intermediate and drug substance CQAs, the ability of the drug substance
123 manufacturing process to remove that impurity should be considered in the assessment. The risk

124 related to impurities can usually be controlled by specifications for raw material/intermediates and/or
125 robust purification capability in downstream steps. The risk assessment can also identify material
126 attributes for which there are inherent limitations in detectability (e.g., viral safety) or inadequate
127 purification capability. In these cases, such upstream material attributes should be considered drug
128 substance CQAs.

129 Using a traditional approach, material specifications and process parameter ranges can be based
130 primarily on batch process history and univariate experiments. An enhanced approach can lead to a
131 more thorough understanding of the relationship of material attributes and process parameters to
132 CQAs and the effect of interactions. Example 1 illustrates the development of process parameters using
133 prior knowledge and chemistry first principles.

134 Risk assessment can be used during development to identify those parts of the process likely to impact
135 potential CQAs. Further risk assessments can be used to focus development work in areas where
136 better understanding of the link between process and quality is needed. Using an enhanced approach,
137 the determination of appropriate material specifications and process parameter ranges could follow a
138 sequence such as the one shown below:

- 139
- Identify potential sources of process variability;
 - Identify the material attributes and process parameters likely to have the greatest impact on drug
140 substance quality. This can be based on prior knowledge and risk assessment tools;
 - Design and conduct experiments and/or mechanistic studies (e.g., multivariate design of
143 experiments, simulations, modelling) to identify and confirm the links and relationships of material
144 attributes and process parameters to drug substance CQAs;
 - Analysis and assessment of the data to establish appropriate ranges, including establishment of a
145 design space if desired.
146

147 Small-scale models can be developed and used to support process development studies. The
148 development of a model should account for scale effects and be representative of the proposed
149 commercial process. A scientifically justified model can enable a prediction of product quality, and can
150 be used to support the extrapolation of operating conditions across multiple scales and equipment.

151 **3.1.6. Design Space**

152 The considerations for design space addressed in ICH Q8 for an enhanced approach to the
153 development of the drug product are equally applicable to drug substance. The ability to accurately
154 assess the significance and effect of the variability of material attributes and process parameters on
155 drug substance CQAs, and hence the limits of a design space, depends on the extent of process and
156 product understanding. In some cases, prior knowledge can be used to support development of a
157 design space. Irrespective of whether the manufacturing process of a product has been developed
158 using prior knowledge the manufacturing process should be appropriately validated (see Process
159 Validation/Evaluation Section 7).

160 For chemical entity design space development, a major focus is knowledge of formation, fate, and
161 purge of impurities through every step of a manufacturing process. It is important to understand the
162 formation, fate (whether the impurity reacts and changes its chemical structure), and purge (whether
163 the impurity is removed via crystallisation, extraction, etc.) as well as their relationship to the resulting
164 impurities that end up in the drug substance as CQAs. All steps (or unit operations) should be
165 evaluated to establish appropriate acceptance criteria for impurities as they progress through multiple
166 process operations.

167 **3.2. Submission of Manufacturing Process Development Information**

168 The information provided on the development of the drug substance manufacturing process (primarily
169 in section 3.2.S.2.6 of the application) should identify significant changes during process development,
170 link relevant drug substance batches with the developmental stage of the manufacturing process used
171 to prepare them, and explain how prior knowledge, risk assessments, and experimental studies (e.g.,
172 modelling, simulations, engineering and scientific principles) were used to establish important aspects
173 of the manufacturing process and control strategy. The significance of a drug substance manufacturing
174 change during development should be assessed by evaluating its potential to impact the quality of the
175 drug substance (and/or intermediate, if appropriate). Process development information should be
176 logically organised and easy to understand. Manufacturers can present process development
177 information in a number of different ways, but some specific recommendations are provided below for
178 consideration.

179 **3.2.1. Overall Process Development Summary**

180 It is recommended that the manufacturing process development section begin with a narrative
181 summary that describes important milestones in the development of the process and explains how
182 they are linked to assuring that the intended quality of the drug substance is achieved. The following
183 should be included in the summary:

- 184 • List of drug substance CQAs;
- 185 • Brief description of the stages in the evolution of the manufacturing process and control strategy;
- 186 • Brief description of the material attributes and process parameters that impact drug substance
187 CQAs;
- 188 • Brief description of the development of any design spaces.

189 Following the Overall Process Development Summary, the manufacturing process development section
190 should include more comprehensive information, as recommended below.

191 **3.2.2. Drug Substance CQAs**

192 The CQAs of the drug substance should be listed, and the rationale for designating these properties or
193 characteristics as CQAs should be provided. In some cases, it might be appropriate to explain why
194 other properties or characteristics that might be considered potential CQAs are not included in the list
195 of CQAs. Links or references should be provided to information submitted elsewhere in the submission
196 (e.g., 3.2.S.3.1, Elucidation of Structure and other Characteristics) that supports the designation of
197 these properties or characteristics as CQAs. Some discussion of drug substance CQAs as they relate to
198 drug product CQAs can be appropriate in the pharmaceutical development section of the application
199 (e.g., 3.2.P.2.1, Components of the Drug Product).

200 **3.2.3. Manufacturing Process History**

201 A description and discussion should be provided of significant changes made to the manufacturing
202 process or site of manufacture of drug substance batches used in support of the marketing application
203 (e.g., those used in nonclinical or clinical studies or stability studies in support of a marketing
204 authorisation) and, if available, production-scale batches. The description should follow a chronological
205 sequence ending with the proposed commercial process.

206 The reason for each significant change should be explained, together with an assessment of its
207 potential to impact the quality of the drug substance (and/or intermediate, if appropriate). Batch
208 information (batch size or scale, site and date of manufacture, route and process used, and intended
209 purpose (e.g., in a specified toxicology or clinical study)) and supporting data from comparative
210 analytical testing on relevant drug substance batches should be provided or referenced (e.g., batch
211 analysis section 3.2.S.4.4).

212 For biotechnological/biological products, the manufacturing process history section should include a
213 discussion of comparability during development as described in ICH Q5E. A discussion of the data,
214 including a justification for selection of the tests and assessment of results, should be included.

215 Testing used to assess the impact of manufacturing changes on the drug substance and the
216 corresponding drug product can also include nonclinical and clinical studies. Cross-reference to the
217 location of these studies in other modules of the submission should be included.

218 **3.2.4. Manufacturing Developmental Studies**

219 The studies and risk assessments used to establish important aspects of the commercial manufacturing
220 process and control strategy cited in the application should be listed (e.g., in tabular form). The
221 purpose or end use of each cited study or risk assessment should be provided.

222 Each cited study or risk assessment should be summarised with a level of detail sufficient to convey an
223 understanding of the purpose of the study, the data collected, how it was analysed, the conclusions
224 reached, and the impact of the study on the manufacturing process or further development of the
225 manufacturing process. The particular parameters and ranges studied should be described and
226 discussed in relation to the proposed operating conditions for the commercial manufacturing process
227 (as described in 3.2.S.2.2). The risk assessment tools and study results on which a design space is
228 based should be adequately described. Example 2 shows a possible communication tool for risk ranking
229 of parameters. Where development refers to specific prior knowledge, the relevant information and
230 data should be provided and, where appropriate, the relevance to the particular drug substance should
231 be justified.

232 Small-scale models used to support process development studies should be described.

233 **4. Description of Manufacturing Process and Process** 234 **Controls**

235 The description of the drug substance manufacturing process represents the applicant's commitment
236 for the manufacture of the drug substance. Information should be provided to adequately describe the
237 manufacturing process and process controls (see ICH M4Q (3.2.S.2.2)).

238 The description of the manufacturing process should be provided in the form of a flow diagram and
239 sequential procedural narrative. The in-process controls for each step or stage of the process should be
240 indicated in the description. Scaling factors should be included for manufacturing steps intended to
241 span multiple operational scales when the process step is scale dependent. Any design spaces in the
242 manufacturing process should be included as part of the manufacturing process description. Example 3
243 gives an example of the presentation of a design space for a biotechnological product.

244 To facilitate the approval of a design space for a complex product, such as a biotechnological/biological
245 product, an applicant can choose to provide information on how movements within the design space
246 will be managed post approval. This could help the reviewer understand how residual risk will be
247 managed.

248 Many biotechnological/biological products have complex upstream processes and use splitting and
249 pooling to create a drug substance. An explanation of how batches of drug substance are defined by
250 the manufacturer (e.g., splitting and pooling of harvests or intermediates), should be provided. Details
251 of batch size or scale and batch numbering should be included.

252 **5. Selection of Starting Materials and Source Materials**

253 **5.1. General Principles**

254 **5.1.1. Selection of Starting Materials for Synthetic Drug Substances**

255 The following general principles should be considered in determining where the drug substance
256 manufacturing process begins (i.e., in selecting starting materials).

- 257 • In general, changes in material attributes or operating conditions that occur near the beginning of
258 the manufacturing process have lower potential to impact the quality of the drug substance;
 - 259 – The relationship between risk and number of steps from the end of the manufacturing process
260 is the result of two factors, one concerning the physical properties of the drug substance and
261 the other concerning the formation, fate, and purge of impurities. The physical properties of a
262 drug substance are determined during the final crystallisation step and subsequent operations
263 (e.g., milling, micronising, transport), all of which occur at the end of the manufacturing
264 process. Impurities introduced or created early in the manufacturing process typically have
265 more opportunities to be removed in purification operations (e.g., washing, crystallisation of
266 isolated intermediates) than impurities generated late in the manufacturing process, and are
267 therefore less likely to be carried into the drug substance. However, in some cases (e.g., when
268 peptides or oligonucleotides are synthesised on a solid support), there is a more limited
269 relationship between risk and number of steps from the end of the manufacturing process;
- 270 • Regulatory authorities assess whether the controls on the drug substance and drug substance
271 manufacturing process can be considered adequate, including whether there are appropriate
272 controls for impurities. To conduct this assessment, enough of the drug substance manufacturing
273 process should be described in the application for regulatory authorities to understand how
274 impurities are formed in the process, how changes in the process could affect the formation, fate,
275 and purge of impurities, and why the proposed control strategy is suitable for the drug substance
276 manufacturing process. This will typically include a description of multiple chemical transformation
277 steps;
- 278 • Manufacturing steps that impact the impurity profile of the drug substance should normally be
279 included in the manufacturing process described in section 3.2.S.2.2 of the application;
- 280 • Each branch of a convergent drug substance manufacturing process begins with one or more
281 starting materials. The GMP provisions described in ICH Q7 apply to each branch beginning with
282 the first use of a starting material. Performing manufacturing steps under GMP together with an
283 appropriate control strategy provides assurance of quality of the drug substance;
- 284 • A starting material should be a substance of defined chemical properties and structure. Non-
285 isolated intermediates are usually not considered appropriate starting materials;
- 286 • A starting material is incorporated as a significant structural fragment into the structure of the drug
287 substance. "Significant structural fragment" in this context is intended to distinguish starting
288 materials from reagents, solvents, or other raw materials. Commonly available chemicals used to
289 create salts, esters or other simple derivatives should be considered reagents.

290 All the general principles above should be considered in selecting Starting Material(s), rather than
291 strictly applying each general principle in isolation (see Example 4).

292 **5.1.2. Selection of Starting Materials for Semi-synthetic Drug Substances**

293 For purposes of this guideline, a semi-synthetic drug substance is one in which the structural
294 constituents have been introduced by a combination of chemical synthesis and elements of biological
295 origin (e.g., obtained from fermentation or by extraction from botanical material). In some cases, it
296 might be appropriate for the applicant to describe the manufacturing process starting from the source
297 material (microorganism or botanical material). However, if it can be demonstrated that one of the
298 isolated intermediates in the synthetic process complies with the principles outlined above for the
299 selection of starting materials for synthetic drug substances, that isolated intermediate can be
300 proposed as the starting material. The applicant should specifically evaluate whether it is possible to
301 analytically characterise the proposed starting material, including its impurity profile, and whether the
302 fermentation or botanical material and extraction process impact the impurity profile of the drug
303 substance. Risks from microbial and other contamination should also be addressed.

304 **5.1.3. Selection of Source Materials for Biotechnological/Biological** 305 **Products**

306 Cell banks are the starting point for manufacture of biotechnological/biologics products. Guidance
307 appropriate for cell banks is contained in ICH Q5A, Q5B, and Q5D.

308 **5.2. Submission of Information for Starting Material or Source Material**

309 Applicants should identify all proposed starting materials or source materials and provide appropriate
310 specifications. Proposed starting materials should be justified.

311 **5.2.1. Justification of Starting Material Selection for Synthetic Drug** 312 **Substances**

313 The applicant should provide a justification for how each proposed starting material is appropriate in
314 light of the general principles for the selection of starting materials outlined above in Section 5.1.1.
315 This can include information on:

- 316 • The ability of analytical procedures to detect impurities in the starting material;
- 317 • The fate and purge of those impurities and their derivatives in subsequent processing steps;
- 318 • How the proposed specification for each starting material will contribute to the control strategy;

319 The applicant should provide, as part of the justification, a flow diagram outlining the current synthetic
320 route(s) for the manufacture of the drug substance, with the proposed starting materials clearly
321 indicated. Changes to the starting material specification and to the synthetic route from the starting
322 material to final drug substance are subject to regional, post-approval change requirements. In
323 addition, regional requirements concerning starting material suppliers may also be applicable.

324 An applicant generally need not justify the use of a commercially available chemical as a starting
325 material. A commercially available chemical is usually one that is sold as a commodity in a pre-
326 existing, non-pharmaceutical market in addition to its proposed use as starting material. Chemicals
327 produced by custom syntheses are not considered to be commercially available. If a chemical from a
328 custom synthesis is proposed as a starting material, it should be justified in accordance with the
329 general principles for the selection of starting materials outlined above in Section 5.1.1.

330 In some instances, additional purification steps might be called for to ensure the consistent quality of a
331 commercially available starting material. In these instances, the additional purification steps should be
332 included as part of the description of the drug substance manufacturing process. Specifications should
333 normally be provided for both incoming and purified starting material.

334 **5.2.2. Justification of Starting Material Selection for Semi-Synthetic Drug** 335 **Substances**

336 If an isolated intermediate is proposed as the starting material for a semi-synthetic drug substance,
337 the applicant should provide a justification that explains how the proposed starting material complies
338 with the general principles for the selection of starting materials outlined above in Section 5.1.1.
339 Otherwise, the applicant should describe the manufacturing process starting from the source material
340 (microorganism or botanical material) and the source materials should be appropriately qualified.

341 **5.2.3. Qualification of Source Materials for Biotechnological/Biological** 342 **Products**

343 Guidance is contained in ICH Q5A, Q5B and Q5D.

344 **6. Control Strategy**

345 **6.1. General Principles**

346 A control strategy is a planned set of controls, derived from current product and process understanding
347 that assures process performance and product quality (ICH Q10). Every drug substance manufacturing
348 process, whether developed through a traditional or an enhanced approach (or some combination
349 thereof), has an associated control strategy.

350 A control strategy can include, but is not limited to, the following:

- 351 • Controls on material attributes (including raw materials, starting materials, intermediates,
352 reagents, primary packaging materials for the drug substance, etc.);
- 353 • Controls implicit in the design of the manufacturing process (e.g., sequence of purification steps
354 (Biotechnological/Biological Products), or order of addition of reagents (Chemical Products));
- 355 • In-process controls (including in-process tests and process parameters);
- 356 • Controls on drug substance (e.g., release testing).

357 **6.1.1. Approaches to Developing a Control Strategy**

358 A control strategy can be developed through a combination of approaches, utilising the traditional
359 approach for some CQAs, steps, or unit operations, and a more enhanced approach for others.

360 In a traditional approach to developing a manufacturing process and control strategy, set points and
361 operating ranges are typically set narrowly based on the observed data to ensure consistency of
362 manufacture. More emphasis is placed on assessment of CQAs at the stage of the drug substance (i.e.,
363 end-product testing). The traditional approach provides limited flexibility in the operating ranges to
364 address variability (e.g., in raw materials).

365 An enhanced approach to manufacturing process development generates better process and product
366 understanding than the traditional approach, so sources of variability can be identified in a more
367 systematic way. This allows for the development of more meaningful and efficient parametric,

368 attribute, and procedural controls. The control strategy might be developed through several iterations
369 as the level of process understanding increases during the product lifecycle. A control strategy based
370 on an enhanced approach can provide for flexibility in the operating ranges for process parameters to
371 address variability (e.g., in raw materials).

372 **6.1.2. Considerations in Developing a Control Strategy**

373 In either the traditional or enhanced approach, the control strategy can include an in-process
374 determination that a CQA is within an appropriate limit, range or distribution in lieu of testing the final
375 drug substance. Any approach other than testing the final drug substance should provide at least the
376 same level of assurance of drug substance quality. When considering such an approach, applicants
377 should determine whether there are any downstream factors that might impact the quality of the drug
378 substance, such as temperature changes, oxidative conditions, light, ionic content, and shear.

379 When developing a control strategy, a manufacturer can consider implementing single or multiple
380 points of control for a specific CQA, depending on the risk associated with the CQA and the ability of
381 individual controls to detect a potential problem. For example, with sterilised drug substances or
382 biotechnological/biological products, there is an inherent limitation in the ability to detect low levels of
383 bacterial or viral contamination in the drug substance. In these cases, end-product testing is
384 considered to provide inadequate assurance of quality, so additional points of control (e.g., attribute
385 and in-process controls) are incorporated into the control strategy.

386 The quality of each raw material used in the manufacturing process should be appropriate for its
387 intended use. Raw materials used in operations near the end of the manufacturing process have a
388 greater potential to introduce impurities into the drug substance than raw materials used upstream.
389 Therefore, manufacturers should evaluate whether the quality of such materials should be more tightly
390 controlled than similar materials used upstream.

391 **6.2. Submission of Control Strategy Information**

392 The information provided on the control strategy should include detailed descriptions of the individual
393 elements of the control strategy plus, when appropriate, a summary of the overall drug substance
394 control strategy. The summary of the overall control strategy can be presented in a tabular format as
395 well as in a diagrammatic format, to aid visualisation and understanding (see Example 5 for example of
396 a Control Strategy Summary in tabular form). Ideally, the summary should explain how the individual
397 elements of the control strategy work together to assure drug substance quality.

398 ICH M4Q recommends that the individual elements of the control strategy reported in an application be
399 provided in the appropriate sections of a submission, including:

- 400 • Description of Manufacturing Process and Process Controls (3.2.S.2.2);
- 401 • Control of Materials (3.2.S.2.3);
- 402 • Controls of Critical Steps and Intermediates (3.2.S.2.4);
- 403 • Container Closure System (3.2.S.6);
- 404 • Control of Drug Substance (3.2.S.4).

7. Process Validation/Evaluation

7.1. General Principles

Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a drug substance or intermediate meeting its predetermined specifications and quality attributes (ICH Q7). Process validation involves the collection and evaluation of data, from the process design stage throughout production, that establish scientific evidence that a process is capable of consistently delivering a quality drug substance.

The drug substance manufacturing process should be validated before commercial distribution of resulting drug product. For biotechnological processes, or for aseptic processing and sterilisation process steps for drug substances, the data provided in support of process validation is included as part of the marketing application (3.2.S.2.5). For non-sterile drug substance processes, results of process validation studies are not normally included in the dossier.

Generally, process validation includes the collection of data on an appropriate number of production batches (see ICH Q7, Section 12.5). The number of batches can depend on several factors including but not limited to: (1) the complexity of the process being validated; (2) the level of process variability; and (3) the amount of experimental data and/or process knowledge available on the specific process.

As an alternative to the traditional process validation, continuous process verification (ICH Q8) can be utilised in process validation protocols for the initial commercial production and for manufacturing process changes for the continual improvement throughout the remainder of the product lifecycle.

7.2. Principles Specific to Biotechnological/Biological Products

For biotechnological/biological products, the information provided in the dossier in support of process validation usually contains both commercial-scale process validation studies and small-scale studies. Process validation batches should be representative of the commercial process, taking into account the batch definition as detailed in the process description

The contribution of data from small-scale studies to the overall validation package will depend upon demonstration that the small-scale model is an appropriate representation of the proposed commercial scale. Data should be provided demonstrating that the model is scalable and representative of the proposed commercial process. Successful demonstration of the suitability of the small-scale model can enable manufacturers to propose process validation with reduced dependence on testing of commercial-scale batches. Data derived from commercial-scale batches should confirm results obtained from small scale studies used to generate data in support of process validation. Scientific grounds, or reference to guidelines which do not require or specifically exclude such studies, can be an appropriate justification to conduct certain studies only at small scale (e.g. viral removal).

Studies should be conducted to demonstrate the ability of the process to remove product-related impurities, process-related impurities (ICH Q6B) and potential contaminants (such as viruses in processes using material from human or animal origin, see ICH Q5A). Studies carried out to demonstrate the lifetime of chromatography columns can include experimental studies carried out in small-scale models but should be confirmed during commercial-scale production.

The limit of in vitro cell age for commercial production should be assessed. ICH documents Q5B and Q5D provide further guidance for relevant products.

447 When platform manufacturing experience is utilised, the suitability of the control strategy should be
448 demonstrated and the drug substance manufacturing process should be appropriately validated at the
449 time of marketing authorisation application. Full scale validation studies should include data derived
450 from the final manufacturing process and site(s) used to produce the product to be commercialised.

451 **8. Submission of Manufacturing Process Development and** 452 **Related Information In Common Technical Documents** 453 **(CTD) Format**

454 The use of an enhanced approach to process development results in the generation of information for
455 which a location in the CTD is not defined. Process development information should usually be
456 submitted in Section 3.2.S.2.6 of the CTD. Other information resulting from development studies could
457 be accommodated by the CTD format in a number of different ways and some specific suggestions are
458 provided below. The applicant should clearly indicate where the different information is located. In
459 addition to what is submitted in the application, certain aspects (e.g., lifecycle management, continual
460 improvement) of this guideline are handled under the applicant's pharmaceutical quality system (see
461 ICH Q10).

462 ***8.1. Quality Risk Management and Process Development***

463 Quality risk management can be used at different stages during process development and
464 manufacturing implementation. The assessments used to guide and justify development decisions
465 (e.g., risk analyses and functional relationships linking material attributes and process parameters to
466 drug substance CQAs) can be summarised in section 3.2.S.2.6.

467 ***8.2. Critical Quality Attributes (CQAs)***

468 The CQAs of the drug substance should be listed, and the rationale for designating these properties or
469 characteristics as CQAs should be provided in the manufacturing process development section of the
470 application (3.2.S.2.6). However, detailed information about structural characterisation studies that
471 supports the designation of these properties or characteristics as CQAs should be provided in the
472 appropriate CTD format sections (e.g., 3.2.S.3.1, Elucidation of Structure and other Characteristics,
473 3.2.S.7 Stability). Some discussion of drug substance CQAs as they relate to drug product CQAs can be
474 appropriate in the pharmaceutical development section of the application (3.2.P.2.1, Components of
475 the Drug Product).

476 ***8.3. Design Space***

477 As an element of the proposed manufacturing process, the design space(s) can be described in the
478 section of the application that includes the description of the manufacturing process and process
479 controls (3.2.S.2.2). If appropriate, additional information can be provided in the section of the
480 application that addresses the controls of critical steps and intermediates (3.2.S.2.4). The
481 manufacturing process development section of the application (3.2.S.2.6) is the appropriate place to
482 summarise and describe process development studies that provide the basis for the design space(s).
483 The relationship of the design space(s) to the overall control strategy can be discussed in the section of
484 the application that includes the justification of the drug substance specification (3.2.S.4.5).

485 **8.4. Control Strategy**

486 The section of the application that includes the justification of the drug substance specification
487 (3.2.S.4.5) is a good place to summarise the overall drug substance control strategy. However,
488 detailed information about input material controls, process controls, and control of drug substance
489 should still be provided in the appropriate CTD format sections (e.g., description of manufacturing
490 process and process controls (3.2.S.2.2), control of materials (3.2.S.2.3), controls of critical steps and
491 intermediates (3.2.S.2.4), drug substance specification (3.2.S.4.1)). The evolution of the control
492 strategy should be described in the manufacturing process development section of the application
493 (3.2.S.2.6).

494 **9. Lifecycle Management**

495 The quality system elements and management responsibilities described in ICH Q10 are intended to
496 encourage the use of science-based and risk-based approaches at each lifecycle stage, thereby
497 promoting continual improvement across the entire product lifecycle. Product and process knowledge
498 should be managed from development through the commercial life of the product up to and including
499 product discontinuation.

500 The development and improvement of a drug substance manufacturing process usually continues over
501 its lifecycle. Manufacturing process performance, including the effectiveness of the control strategy and
502 suitability of any design spaces, should be periodically evaluated. This can be done as part of the
503 Product Quality Review described in ICH Q7 Section 2.5. Knowledge gained from this product quality
504 review, as well as from the manufacturing of the drug substance for commercial supply, can be used to
505 further improve process understanding and process performance and to adjust the control strategy to
506 ensure drug substance quality. Knowledge gained from other products, or from new innovative
507 technologies, can also contribute to these goals. Continual improvement and successful process
508 validation, or continuous process verification, call for an appropriate and effective control strategy.

509 There should be a systematic approach to managing knowledge related to both drug substance and its
510 manufacturing process throughout the lifecycle. This knowledge management should include but not be
511 limited to process development activities, technology transfer activities to internal sites and contract
512 manufacturers, process validation studies over the lifecycle of the drug substance, and change
513 management activities. The knowledge and process understanding should be shared across all sites
514 involved in manufacturing the drug substance (ICH Q10 1.6.1).

515 An applicant can include in the original submission a proposal for how specific future changes will be
516 managed during the product lifecycle. For an example of how process parameters can be managed for
517 a biotechnological product, see Example 2.

518 Any proposed change to the manufacturing process should be evaluated for the impact on the quality
519 of drug substance and, when appropriate, drug product. This evaluation should be based on scientific
520 understanding of the manufacturing process and should determine appropriate testing to analyse the
521 impact of the proposed change. For chemical entities the appropriate testing to analyse the impact of
522 the proposed change could, for example, be on an intermediate or drug substance. For process
523 changes for biotechnological/biological products, see also ICH Q5E.

524 All changes should be subject to internal change management processes as part of the overall Quality
525 System. This includes movements within the Design Space, which do not require approval by regional
526 regulatory authorities.

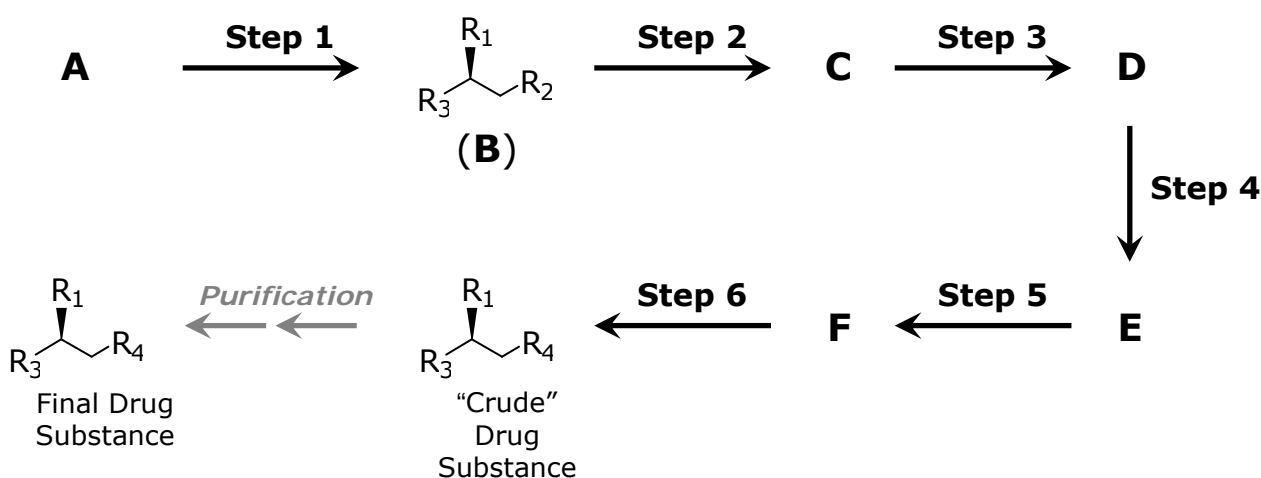
527 Changes to information filed and approved in a dossier should be reported to regulatory authorities in
528 accordance with regional regulations and guidelines.

529 10. Illustrative Examples

530 These examples are provided for illustrative purposes and only suggest potential uses. This Appendix is
531 not intended to create any new expectations beyond the current regulatory requirements.

532 10.1. Example 1: Linking Material Attributes and Process Parameters to 533 Drug Substance CQAs - Chemical Entity

534 This example illustrates development of a design space using prior knowledge and chemistry first
535 principles. It depicts both a traditional and enhanced approach to determination of the ranges for
536 parameters controlling the formation of a hydrolysis impurity during Step 5 of the following reaction
537 scheme (Also used in Example 4).



538

539 After the formation of intermediate **F** in Step 5, the mixture is heated to reflux. During reflux an
540 impurity is formed through hydrolysis of intermediate **F**.

541 For the purpose of this simplified example, this is the only reaction of intermediate **F** that occurs during
542 this reflux. The following assumptions were used in the design of the process:

- 543
- The concentration of intermediate **F** remains approximately constant.
 - Temperature remains constant.
 - The acceptance criterion for the hydrolysis impurity in Intermediate **F** is 0.30%. (This is based on the CQA in the drug substance and the demonstrated capacity of the subsequent steps to purge the impurity.)
 - The initial amount of water in the reflux mixture depends on the amount of water in Intermediate **E**, which can be controlled by drying.
- 548

550 Time of reflux and water concentration were identified as the most important parameters affecting the
551 hydrolysis of intermediate **F**. Other potential factors were determined to be insignificant based on prior
552 knowledge and risk assessment.

553

554

555 The reaction was expected to follow second-order kinetics according to the equation below:

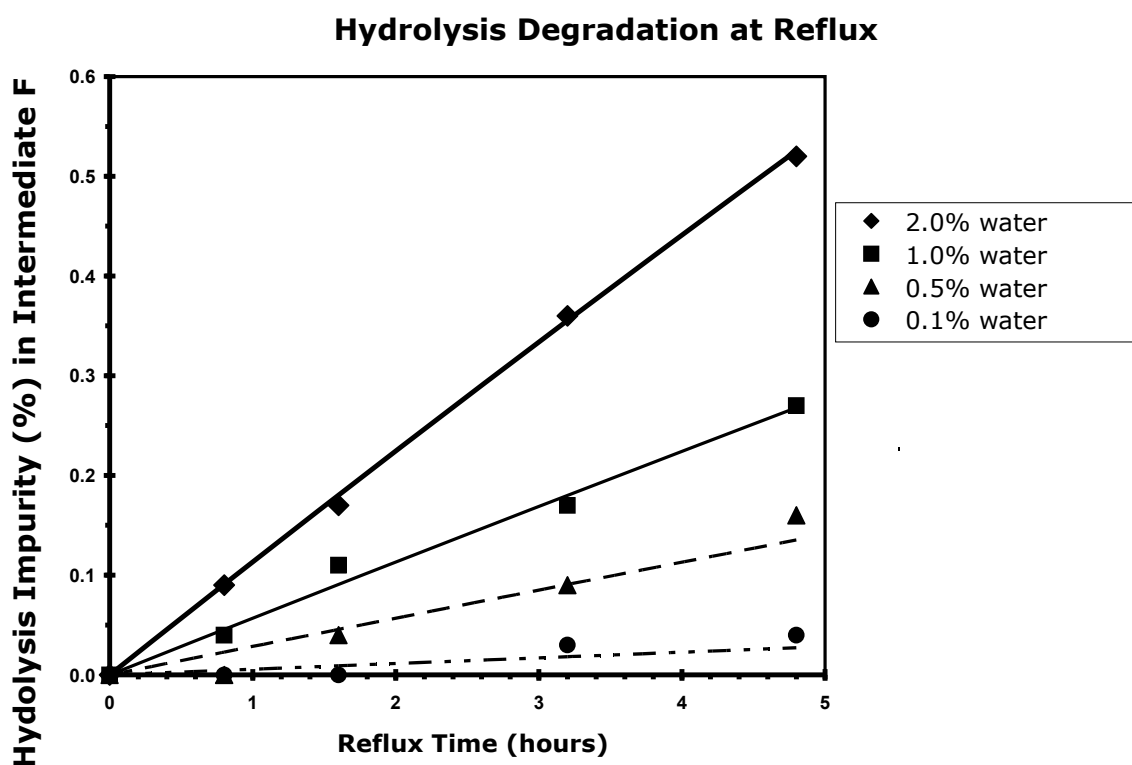
556

557
$$\frac{d[\text{hydrolysis_impurity}]}{dt} = k[H_2O][F]$$

558 Where $[F]$ refers to the concentration of intermediate **F**.

559 Through simple experimentation the following graph linking the extent of hydrolysis to time and the
560 water content of intermediate **E** can be generated:

561



562

563 Traditional Approach:

564 In a traditional approach this information would be used to set a proven acceptable range for % water
565 and time that achieves the acceptance criteria for the hydrolysis impurity of 0.30% in intermediate **F**.
566 This is typically done by setting a target value and maximum such as:

- 567
- Dry Intermediate **E** to a maximum water content of 1.0%
 - Target reflux time of 1.5 hours and a maximum reflux time of 4 hours
- 568

569 Enhanced Approach:

570 The 2nd order rate equation can be integrated and solved explicitly (Chemical Reaction Engineering,
571 Levenspiel 2nd Edition, 1972).

572
$$\ln\left(\frac{M - X_F}{M(1 - X_F)}\right) = ([H_2O]_0 - [F]_0)kt$$

573 Where:

$[F]_o$ refers to the initial concentration of intermediate **F**,

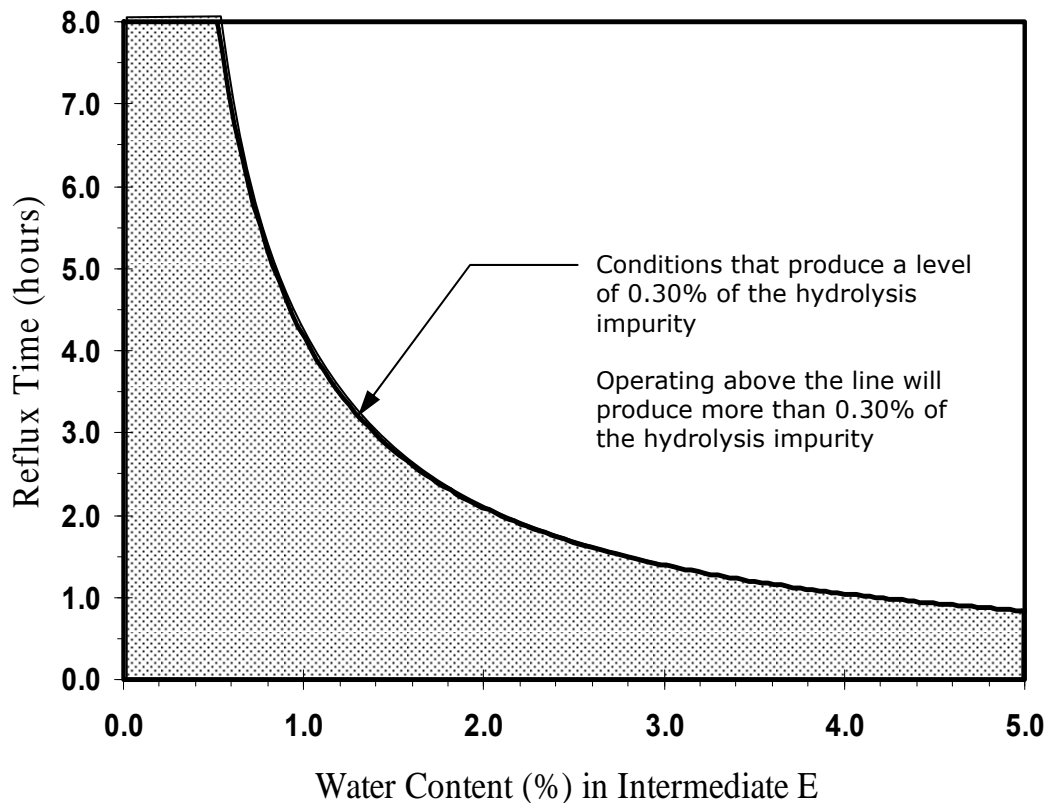
$[H_2O]_o$ refers to the initial concentration of water,

$M = [F]_o/[H_2O]_o$ refers to the ratio of the initial concentration of intermediate **F** to the initial concentration of water, and

X_F refers to the time-dependent concentration of the hydrolysis degradant of intermediate **F**.

574 Solving this equation for time (t) permits the calculation of the maximum allowable reflux time for any
575 combination of initial water content and target level for the hydrolysis impurity. (The initial
576 concentration of intermediate **F** in the reflux mixture will essentially be constant from batch to batch.)
577 The following graph shows the combination of conditions required to ensure that the hydrolysis
578 impurity remains below 0.30% in intermediate **F**.

Interdependence of Reflux Time and Water Content in the Formation of Hydrolysis Impurity



579

580 The area below the line in the plot above could be proposed as the design space.

581 Summary:

582 While both the traditional and enhanced approach provide ranges of water content and time to control
583 the formation of the hydrolysis impurity, the enhanced approach allows more manufacturing flexibility.

584 **10.2. Example 2: Use of Quality Risk Management to Support Lifecycle**
585 **Management of Process Parameters**

586 This example illustrates how results from an iterative quality risk assessment can be used to
587 communicate the rationale for classification and proposed future management of changes to process
588 parameters. Relevant parameters for establishment of a design space for a Q-anion exchange column
589 are shown in this Risk Ranking Histogram. The histogram showing the ranking of parameters is
590 intended for illustrative purposes only and is not all inclusive, nor is it meant to be applicable to all
591 products that may use ion exchange chromatography.

592 Initial Filing

593 A quality risk assessment utilising prior knowledge and development studies can be used to rank
594 process parameters based on their relative potential to have an effect on product quality if parameter
595 ranges were changed. The histogram shows the potential impact to quality for future changes to
596 parameter ranges based on the knowledge and understanding at the time of submission. Process
597 development studies and interaction studies were conducted to establish design space boundaries for
598 each of the higher risk parameters (parameters A-F) that impact CQAs. Parameters G, H and I were
599 also challenged in the development studies and shown not to impact CQAs under the conditions
600 studied. Changes to the ranges of these parameters could still carry residual risk (based on prior
601 knowledge/uncertainties, including potential scale sensitivity). Parameters J-T were considered lower
602 risk parameters based on documented prior knowledge, and therefore an impact on quality attributes
603 is not anticipated. The ranking of parameters from the quality risk assessment can be used to
604 communicate with regulators regarding a lifecycle management approach to assure continual
605 improvement throughout the product lifecycle.

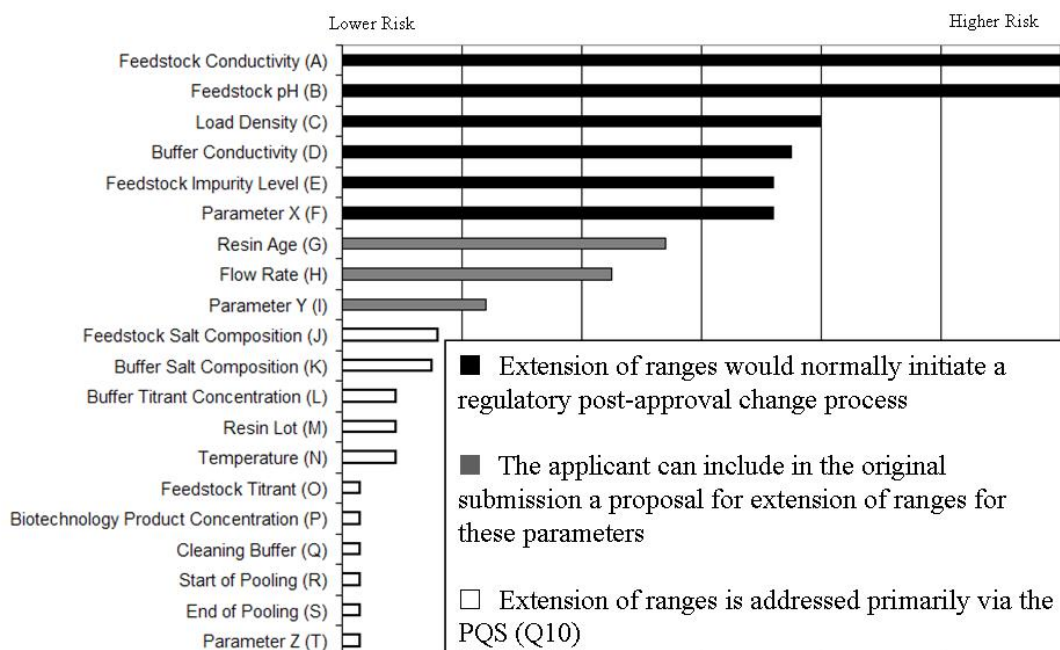
606 Lifecycle Management Options

607 Risk should be reassessed throughout the lifecycle as process understanding increases.
608 Recommendations regarding lifecycle management changes can be found in the Pharmaceutical Quality
609 System (PQS) as described in ICH Q10.

610 Working within the design space is not considered as a change. Movement out of the design space is
611 considered to be a change and consequently any extension of ranges for higher risk parameters (i.e.
612 parameters A-F) would normally initiate a regulatory post approval change process.

613 An applicant can include in the original submission a proposal for how specific future changes to
614 parameters G, H, and I will be managed during the product lifecycle. Extension of ranges for lower
615 risk parameters (J-T) does not require prior regulatory approval, although notification may be called
616 for depending on regional regulatory requirements and guidance. If it is determined subsequently to
617 the filing that there is a change in the risk ranking, such that an extension of ranges for a parameter
618 represents a higher risk, this change should be appropriately filed through the regional regulatory
619 process.

Risk Ranking of Ion Chromatography Process Parameters



620

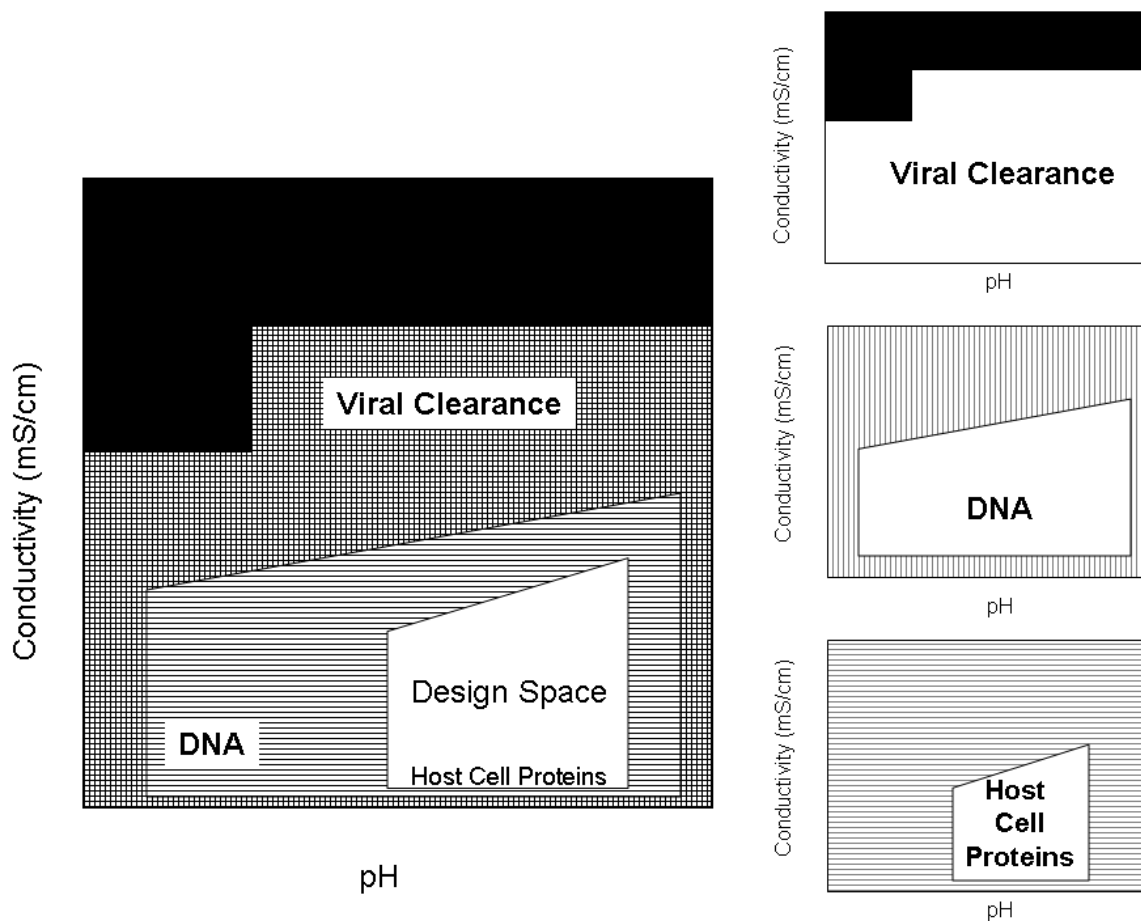
621 **10.3. Example 3: Presentation of a Design Space for a Biotechnological**
 622 **Product Unit Operation**

623 This example is based on a design space for a drug substance purification unit operation (Q-anion
 624 exchange column run for a monoclonal antibody in flow-through mode), determined from the common
 625 region of successful operating ranges for multiple CQAs. This figure illustrates a potential depiction of a
 626 design space based on successful operating ranges for three CQAs and the use of prior knowledge
 627 (platform manufacturing) in developing a design space. The ranges represented here indicate areas of
 628 successful operation and not edges of failure.

629 Viral clearance and host cell protein (HCP) ranges were derived from multivariate experimentation (see
 630 ICH Q8). The successful operating range for DNA was derived from prior knowledge (platform
 631 manufacturing) which in turn was derived from results of multivariate studies performed on related
 632 products. The successful operating range for HCP lies within the viral clearance and DNA successful
 633 operating ranges. In this example, the diagrams below show how HCP limits the unit operation design
 634 space compared to viral safety and DNA. Consideration of additional input variables, process
 635 parameters, or CQAs could limit design space further.

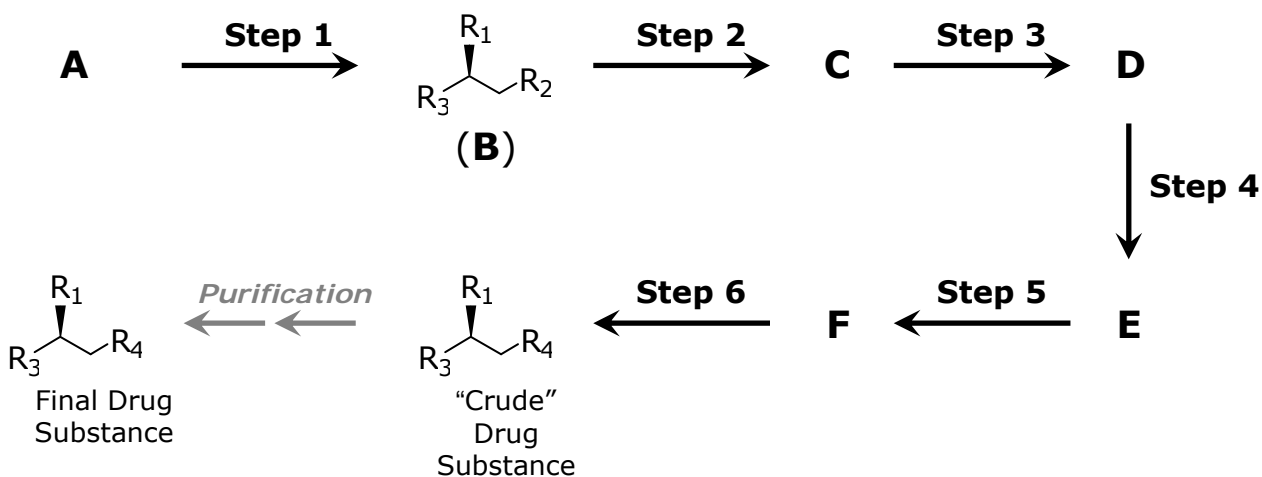
636 The design space is applicable only within specified conditions, including

- 637 1. Appropriately defined quality criteria for input materials;
 638 2. Appropriately selected CQAs and process parameters.



639

640 **10.4. Example 4: Selecting an Appropriate Starting Material**



641

642 This example illustrates the importance of considering all general principles described in section 5.1.1
 643 when selecting an appropriate starting material, rather than applying each general principle in
 644 isolation. The example is fictional, based on a linear synthesis for a relatively simple molecule, and is
 645 not intended to convey any particular meaning in relation to the number of steps.

646 The desired stereochemical configuration in the drug substance results from the synthesis of compound
 647 **B** in step 1 from a commercially available achiral precursor **A** and a stereo-selective reagent. A small
 648 amount of the opposite enantiomer of compound **B** is also formed in step 1. Once formed, both

649 stereochemical configurations persist through the synthetic steps that follow, so the drug substance
650 also contains a small amount of its undesired enantiomer as a specified impurity. In accordance with
651 the principle that manufacturing steps that impact the drug substance impurity profile should normally
652 be included in the manufacturing process described in section 3.2.S.2.2 of the application, it could be
653 concluded that step 1 should be described in 3.2.S.2.2, and that **A** should be considered the starting
654 material.

655 However, for this manufacturing process, it is also known that all of the significant impurities in the
656 drug substance (other than opposite enantiomer) arise from steps 4, 5, and 6. Steps 2 and 3 have no
657 impact on the drug substance impurity profile, and the only impact from step 1 is with regard to the
658 enantiomeric impurity. Furthermore, it is also known that the stereocentre first formed in step 1 is
659 stable to the manufacturing conditions in all of the steps that follow (i.e., no racemisation occurs or is
660 ever likely to occur), and that a suitable analytical procedure exists for measuring the amount of the
661 opposite enantiomer in compound **D**. Therefore, as compound **D** is in accordance with most of the
662 other general principles described in section 5.1.1, it would be reasonable to propose **D** as the starting
663 material instead of **A** in accordance with the principle that early steps in the manufacturing process
664 tend to have a lower potential to impact drug substance quality than later steps. In this example, the
665 only impact of step 1 is on the amount of the enantiomeric impurity in the drug substance, and this
666 could alternatively be controlled through an appropriate limit on the amount of the opposite
667 enantiomer in compound **D**. Information on steps 1-3 would be made available to regulatory
668 authorities in order to justify such a proposal as per regional expectations.

669 A similar argument could be made if the stereocentre in the drug substance originated in the
670 commercially available precursor **A** instead of being created in step 1.

671 ***10.5. Example 5: Summary of Control Elements for select CQAs***

672 This example illustrates how part of a drug substance control strategy might be summarised in tabular
673 form. The tables show how an applicant can communicate information on multiple elements of a drug
674 substance control strategy and guide the reviewer to sections of the CTD where detailed elements of
675 the control strategy are described or justified. Such control strategy summary tables should not
676 contain the rationale or justification for the controls but should simply indicate where the information
677 can be found in the application for marketing authorisation.

678 There are multiple ways of presenting this information, and two are shown below. One table shows
679 more detail than the other to illustrate that there is a range of possibilities for presenting this
680 information. The amount of detail included in a control strategy summary table is up to the applicant
681 and is not related to the type of drug substance. CQAs and control elements shown in the tables below
682 are only examples and are not intended to be a comprehensive representation of all elements of a drug
683 substance control strategy. The tables should not be considered templates. The section of the
684 application that includes the justification of the drug substance specification (3.2.S.4.5) is a good place
685 to summarise the overall drug substance control strategy.

686 5a. Example of a Possible Control Strategy Summary – Biotechnological Products

Drug Substance CQA	Control Strategy for drug substance CQA	Section(s) in CTD where detailed information is located
Contaminants in biologically sourced materials (Viral Safety)	Summaries of viral safety information for biologically-sourced materials	3.2.S.2.3
	Detailed information including for materials of biological origin, testing at appropriate stages of production and viral clearance studies	3.2.A.2
Residual Host Cell Proteins	Design Space for an individual unit operation (e.g. see Example 3)	3.2.S.2.2
	Target range for consistent removal assured by validation	3.2.S.2.5
	Analytical procedures and their validation	3.2.S.4.2 and 3.2.S.4.3
Specific Glycoforms	Controls implicit in the design of the manufacturing process including a summary of process control steps (e.g. cell culture conditions, downstream purification, holding conditions etc.)	3.2.S.2.2
	Characterisation to justify classification as CQA (cross reference to non-clinical/clinical sections if relevant)	3.2.S.3.1
	Control of Critical Steps, Testing program and specifications	3.2.S.2.4 and/or 3.2.S.4.1
	Justification of specification	3.2.S.4.5
	Stability	3.2.S.7

687

688 5b. Example of a possible Control Strategy Summary – Chemical Entity.

Drug Substance CQA (3.2.S.2.6) / Limit in Drug Substance↓	Type of Control →	In process Controls (including In-process testing and process parameters)	Controls on material attributes (raw materials/starting materials /intermediates)	Impact of Manufacturing Process Design	Is CQA tested on drug substance/ included in Drug Substance specification (3.2.S.4.1)
Organic Purity					
Impurity X NMT 0.15%		Design space of the reflux unit operation composed of a combination of %water in Intermediate E and the reflux time in step 5 that delivers Intermediate F with Hydrolysis Impurity ≤0.30% (3.2.S.2.2)			Yes/Yes
Impurity Y NMT 0.20%		Process parameters step 4 (3.2.S.2.2) p(H ₂) ≥2 barg T <50°C In-process test step 4 (3.2.S.2.4) Impurity Y ≤0.50%			Yes/Yes
Any individual unspecified impurity NMT 0.10%			Specs for starting material D (3.2.S.2.3)		Yes/Yes
Total impurities NMT 0.50%					Yes/Yes
Enantiomeric purity S-enantiomer NMT 0.50%			Spec for starting material D (3.2.S.2.3) S-enantiomer ≤0.50%	Stereocentre is shown not to racemize; (3.2.S.2.6)	No/No
Residual Solvent					
Ethanol NMT 5000 ppm		In-process test during drying after final purification step (3.2.S.2.4) LOD ≤0.40 %		In-process results correlated to test results on drug substance.	No/Yes

Type of Drug Substance CQA (3.2.S.2.6) / Limit in Drug Substance↓	In process Controls (including In-process testing and process parameters)	Controls on material attributes (raw materials/starting materials /intermediates)	Impact of Manufacturing Process Design	Is CQA tested on drug substance/ included in Drug Substance specification (3.2.S.4.1)
Toluene NMT 890 ppm	In-process test step 4 (3.2.S.2.4) ≤2000 ppm by G.C		(3.2.S.2.6) Process steps after step 4 are shown to purge toluene to levels significantly below (less than 10%) that indicated in ICH Q3C (3.2.S.2.6).	No/No ¹

689 1This approach could be acceptable as part of a control strategy when justified by submission of relevant process data that confirms the adequacy of the
690 process design and control. The manufacturing process should be periodically evaluated under the firm's quality system to verify removal of the solvent.

691 Notes concerning Table 5b

692 The above table is based on the route of synthesis presented in Example 1. The Control for
693 enantiomeric impurity is based on Decision Tree 5 from ICH guideline Q6A, which allows for control of
694 chiral quality to be established by applying limits to appropriate starting materials or intermediates
695 when justified from development studies. In order for this approach to be acceptable data would need
696 to be provided in 3.2.S.2.6 to demonstrate the stability of the stereocentre under the proposed
697 manufacturing conditions.

698 The table summarises only a portion of the control strategy that would be presented at the time of
699 initial submission and does not include all CQAs of the drug substance. The example control strategy
700 provides for control of some CQAs at stages in the process prior to the drug substance. The elements
701 of the proposed control strategy described in the application would be justified by the applicant in
702 3.2.S.4.5 and subject to regulatory assessment and approval.

703 **11. Glossary**

704 Chemical Transformation Step

705 For Chemical Entities, a step involved in the synthesis of the chemical structure of the drug substance
706 from precursor molecular fragments. Typically it involves C-X or C-C bond formation or breaking.

707 Continuous Process Verification: An alternative approach to process validation in which manufacturing
708 process performance is continuously monitored and evaluated. (ICH Q8)

709 Control Strategy: A planned set of controls, derived from current product and process understanding,
710 that assures process performance and product quality. The controls can include parameters and
711 attributes related to drug substance and drug product materials and components, facility and
712 equipment operating conditions, in-process controls, finished product specifications, and the associated
713 methods and frequency of monitoring and control. (ICH Q10)

714 Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or
715 characteristic that should be within an appropriate limit, range, or distribution to ensure the desired
716 product quality. (ICH Q8)

717 Design Space: The multidimensional combination and interaction of input variables (e.g., material
718 attributes) and process parameters that have been demonstrated to provide assurance of quality.
719 Working within the design space is not considered as a change. Movement out of the design space is
720 considered to be a change and would normally initiate a regulatory post approval change process.
721 Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH
722 Q8)

723 Intermediate: See ICH Q7, ICH Q3a, and ICH Q5c

724 Impurity: See ICH Q6A and ICH Q6B

725 Lifecycle: All phases in the life of a product from the initial development through marketing until the
726 product's discontinuation (ICH Q8).

727 Platform Manufacturing: The approach of developing a production strategy for a new drug starting
728 from manufacturing processes similar to those used by the same applicant to manufacture other drugs
729 of the same type (e.g., as in the production of monoclonal antibodies using predefined host cell, cell
730 culture, and purification processes, for which there already exists considerable experience)

731 Process Robustness: Ability of a process to tolerate variability of materials and changes of the process
732 and equipment without negative impact on quality. (ICH Q8)

733 Quality Risk Management (QRM): A systematic process for the assessment, control, communication
734 and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)

735 Quality Target Product Profile (QTPP): A prospective summary of the quality characteristics of a drug
736 product that ideally will be achieved to ensure the desired quality, taking into account safety and
737 efficacy of the drug product. (ICH Q8)

738 Real Time Release Testing: The ability to evaluate and ensure the quality of in-process and/or final
739 product based on process data, which typically include a valid combination of measured material
740 attributes and process controls. (ICH Q8)